Prospective Randomized Controlled Study comparing Conventional Surgery and Ultrasound guided Foam Sclerotherapy for the Treatment of Primary Superficial Venous Insufficiency of Lower limbs.

CERTIFICATE

This is to certify that the thesis entitled “Prospective Randomized Controlled Study comparing Conventional Surgery and Ultrasound guided Foam Sclerotherapy for the Treatment of Primary Superficial Venous Insufficiency of Lower limbs” is based on the work carried out by Dr. Raguram G in partial fulfillment of the requirements for MS (Branch I) General Surgery examination of the Tamil Nadu Dr. MGR Medical University to be held in March 2008.

The candidate has independently reviewed the literature and carried out the techniques towards completion of the thesis. This thesis has not been submitted for the award of any degree or diploma of any other University.

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A thesis submitted to the Tamil Nadu Dr. M.G.R. Medical University in partial fulfillment of the degree MS (Branch 1) General Surgery

By Raguram G, Christian Medical College, Vellore,
Tamil Nadu. 632004. India

1.0 Introduction

The problem of varicose veins and venous ulcer has plagued mankind since prehistoric times. It is one of the many prices he had to pay for gaining an erect posture. Though we have achieved cure for various diseases, till now no permanent cure has been found for venous insufficiency. Surgery has been the gold standard for treating chronic venous insufficiency. The challenge for the surgeon dealing with varicose veins has always been balancing a cosmetically acceptable result with a low incidence of recurrence and complications. Increasingly well-informed patients who pressure the treating surgeon for cosmetically acceptable results in conjunction with expansion of minimally invasive techniques have made the treatment of superficial venous reflux and varicose veins a rapidly evolving field.[1]

New, minimally invasive techniques for the treatment of varicose veins including Radio frequency ablation (RFA), Endovenous laser therapy (EVLT), and Transilluminated power phlebectomy (TIPP) represent effective and possibly superior alternatives to traditional saphenous vein stripping and stab avulsion of varicose veins. [1]

Sclerotherapy can improve the cosmetic appearance of aberrant blood vessels and greatly benefit symptomatic veins by decreasing pain, burning, and cramps that many patients describe. Resolution of larger varicosities can improve the risk

of further venous disease sequelae. Sclerotherapy continues to be the gold standard in the treatment of lower extremity small vessel disease.[2] The results of using liquid sclerosant for large veins were poor. After the use of foam sclerotherapy for large veins, the recurrence rates have come down. The availability of a simple method to create foam, proposed by Tessari, has made foam sclerotherapy popular. The safety of foam sclerotherapy has been proven in large scale studies. The recurrence rates following foam sclerotherapy has been comparable to surgery.

So far no randomised controlled trial has compared ultrasound guided sclerotherapy with surgery. Therefore this study was carried out to compare the efficacy of foam sclerotherapy when compared to surgery.

2.0 Aims and Objectives

1. To assess the obliteration of superficial venous system following conventional surgery and ultrasound guided foam sclerotherapy at the end of 3 months.

2. To compare the clinical outcome following conventional surgery and ultrasound guided foam sclerotherapy at the end of 3 months.

3. To compare the cost of the conventional surgery and ultrasound guided foam sclerotherapy for the treatment of chronic venous insufficiency.

3.0 Review of Literature

3.1 Background

Chronic venous insufficiency is a very common problem leading to recurrent ulceration in lower limbs and causes significant morbidity and increases healthcare costs. Commonly reported symptoms include local discomfort over varicosities (pain, burning discomfort, aching and itching), generalized lower limb symptoms (aching, heaviness, swelling and restless leg syndrome) and nocturnal cramps, as well as complaints about cosmetic appearance. Women are more prone to these symptoms due to hormonal influences.[3] Swelling and night cramps are commonly reported symptoms of varicose veins in pregnancy. There is little correlation between symptoms of varicose veins and their extent or size on examination.

Though surgery has been the gold standard for the treatment of chronic venous insufficiency, it does have risk of recurrence and associated morbidity. Recently many minimally invasive methods with lower morbidity and equally good results have been used. Of all the newer methods, ultrasound guided foam sclerotherapy is the cheapest and simplest method with good result.

3.2 History

Surgery is commonly used to treat 'main stem' varicose veins. Sclerotherapy has been used to treat varicose veins from as early as 1835 according to records from Massachusetts General Hospital. Chassaignac, who published a series of cases from 1853 injected zinc chloride into varicose veins.[4] Hobbs gave a historical overview on the use of sclerotherapy and compression bandaging in the early part of the 20th century, starting in Paris with Linser (1911) and Sicard (1911).[5]

Orbach,[6] proposed the use of foam in 1944, generated by the simple process of shaking a sclerosant solution in a syringe with air. This produced foam with large bubbles and a high air-liquid ratio, which proved to be effective for smaller veins but not larger veins. However, it was not until 1963 that the technique of sclerotherapy was described and popularised by Fegan, whose name has become synonymous with the procedure.[7] The interest in sclerotherapy plateaued in the 1980s, as the state of the art stagnated. Then in 1993, Juan Cabrera, began using a microfoam preparation of sodium tetradecyl sulfate and polidocanol for sclerotherapy. It represented a revolution in the treatment of venous diseases. [8]

A 1998 survey on behalf of the Vascular Surgical Society of Great Britain and Ireland showed that most surgeons reserved sclerotherapy for either primary varicose veins in the absence of superficial venous incompetence (69.7%) or residual varicose veins following surgery (77.1%).[9] In 1997, Monfreux described foam produced with air in a glass syringe. The foam produced was quite durable but composed of relatively large bubbles. This method also required a learning

period to consistently produce high-quality foam. The large bubbles easily spread along the vessels and caused temporary patient dizziness or confusion at times.

Other researchers soon developed other forms of foam with proven efficacy. Most recently, Frullini and Cavezzi[10] and Tessari et al[11] have described other variations in the production of foam. The Tessari method is now one of the most popular techniques, using 2 ordinary disposable syringes attached to a 3-way stopcock. Its popularity can be attributed to the simplicity and low cost of the method, and the production of high-quality foam. Several large series have been published to document the efficacy and safety of foam sclerotherapy.[11,12]

A 10-year, prospective, controlled, randomized trial involving over 800 patients conducted by vascular surgeons in Europe compared 6 treatment options for varicose veins: liquid sclerotherapy, high-dose liquid sclerotherapy, multiple ligations, stab avulsion, foam sclerotherapy, and ligation followed by sclerotherapy.[12] The report concluded that foam sclerotherapy appears to be more effective than standard-dose liquid sclerotherapy, and results can be comparable to surgery. Interestingly, this study also looked at lung scintigraphy in select patients who received foam. The investigators found no perfusion defect even after injections of up to 10 mL of foam.[12] Although foam sclerotherapy is effective for veins of all sizes, some researchers have noted a slightly higher rate of minor adverse effects such as pigmentation, inflammation, and minimal necrosis when foam is used for small reticular veins and telangiectasias.[10]

A recent randomized trail found that ultrasound guided foam sclerotherapy combined with sapheno-femoral ligation was less expensive, involved a shorter treatment time and resulted in more rapid recovery compared to sapheno-femoral ligation, saphenous stripping and phlebectomies. [13]

3.3 Chronic venous insufficiency

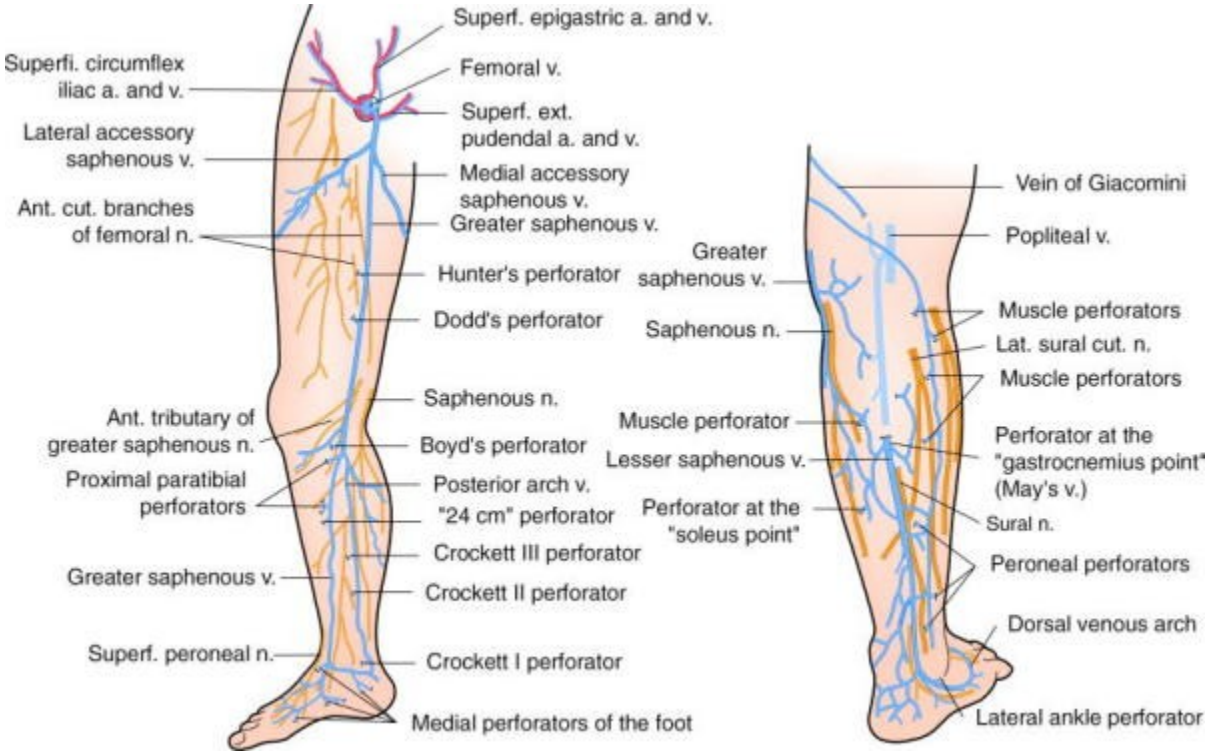
3.3.1 Epidemiology

Varicose veins are a common finding with a point prevalence of 20 to 25% in females and 10 to 15% in males over the age of 15 years. [14] It is difficult to find a satisfactory definition of varicose veins upon which consensus has been reached. Minor venous abnormalities such as thread veins are also seen in up to 50 to 55% of women and 40 to 50% of men.

The symptoms attributable to varicose veins, and their correlation with the extent of venous reflux, are not clearly defined. Epidemiological evidence suggests that even in the presence of 'main stem' varicose veins, most lower limb symptoms have a non-venous cause[2]. The Edinburgh Vein Study has demonstrated superficial venous reflux in 9% of randomly selected men and 15% of women as well as deep venous reflux in 22% of men and 11% of women.[15]

3.3.2 Normal Venous Anatomy and Function

Fig 1. Normal Venous Anatomy



The veins of the lower extremity are divided into the superficial and deep venous system connected by a series of perforator veins.[16]

The superficial venous system is located above the muscular fascial layer. It comprises an interconnecting network of veins, which serve as the primary collecting system, and several truncal superficial veins, which function as a conduit

to return blood to the deep venous system. The principal named superficial veins of the lower extremity are the short (or lesser) saphenous vein, which runs from the ankle typically to join the popliteal vein at the saphenopopliteal junction, and the great saphenous vein, which runs from the ankle to join the common femoral vein at the saphenofemoral junction. Other superficial veins, including the posterior arch, lateral accessory saphenous, and vein of Giacomini, also can develop pathology leading to CVI.

The deep venous system is located below the muscular fascia and serves as collecting veins and the outflow from the extremity. The deep veins of the lower extremity consist of axial veins, which follow the course of the major arteries, and the intramuscular veins. Venous sinusoids within the leg muscles coalesce to form intramuscular venous plexi. The paired calf veins, corresponding to the axial arteries, merge to form a single large popliteal vein. The popliteal vein, on passing through the adductor canal, is subsequently known as the femoral (often called the superficial femoral) vein. The femoral vein is joined by the profunda femoris (or deep femoral) vein in the upper thigh to form the major outflow of the leg, the common femoral and eventually the external iliac vein. The superficial veins are connected to the deep venous system by a number of perforating veins in the thigh and leg that pass through anatomic fascial spaces.

A series of bicuspid valves are located throughout the deep and superficial veins and ensures that blood moves in the cephalad direction, preventing the return of

blood toward the feet while in the upright posture. The first of these lower-extremity valves is usually located in the common femoral vein or less commonly in the external iliac vein. The frequency of venous valves increases from the proximal to the distal leg to prevent an increase in pressure within the distal veins resulting from the effects of gravity. Perforating veins also contain one-way valves that prevent reflux of blood from the deep veins into the superficial system.

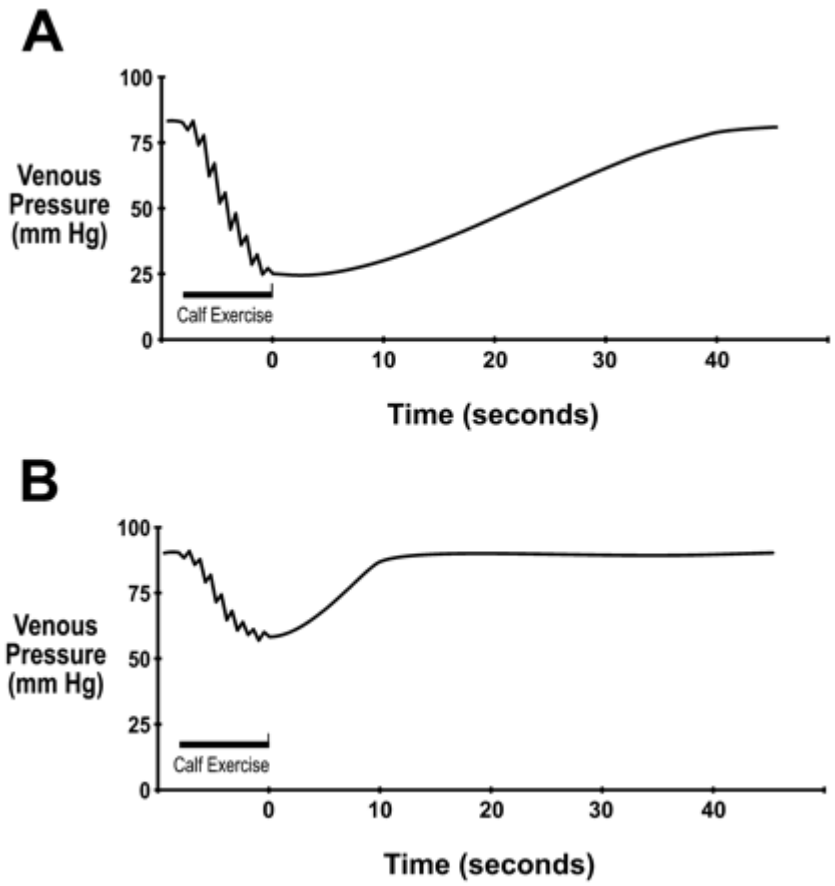
The valves function in concert with venous muscle pumps to allow the return of blood against gravity to the heart. Contraction of the muscle pumps primarily in the calf, but also in the foot and thigh, and forces blood out of the venous plexi and up the deep venous system because of increased pressure within the fascial compartments. The valve system prevents blood from being forced distally within the deep venous system or through the perforator system into the superficial system. Immediately after ambulation, the pressure within the veins of the lower extremity is normally low (15 to 30 mm Hg) because the venous system has been emptied by the muscle pump function (Figure 1). Relaxation of the muscle pump then allows blood to return to the deep venous system via arterial inflow through the superficial and the distal deep venous systems. With prolonged standing, the veins slowly fill and become distended, allowing the valves to open and eventually increase pressure that is directly related to the height of the column of blood. Contraction of the muscle pump will again empty the veins and reduce venous pressure.

3.3.3 Pathophysiology: The macrocirculation

Signs and symptoms of chronic venous insufficiency (CVI) result from venous obstruction, venous reflux, calf muscle pump dysfunction, or combinations of these factors. In most cases, reflux is the principal cause. Venous insufficiency is described as primary or secondary. Primary valvular incompetence is the diagnosis when no obvious etiologic mechanism of valvular dysfunction canbe identified. Such cases may develop from a loss of elasticity of the vein wall.[17] Valvular incompetence is described as secondary when there is an obvious antecedent event, most frequently a deep venous thrombosis (DVT)

Ambulatory venous pressure (AVP) is the simplest and direct measure of venous hypertension. Patients with AVP of below 40 mmHg have minimal incidence of venous ulceration. Venous recovery time (VRT) has also been used as indicator of valve dysfunction.

Fig 2. Illustrative ambulatory venous pressure measurements. (A) Normal venous pressure. The resting standing venous pressure is ≈80 to 90 mm Hg. The pressure drops with calf exercise to ≈20 to 30 mm Hg, or a >50% decrease. The return in pressure is more gradual, with refill taking >20 s. (B) Abnormal venous pressure with deep venous reflux. The drop in pressure with exercise is blunted (<50% decrease). The return in venous pressure to the resting level is rapid because of a short refill time (<20 s).



3.3.4 Microciculatory abnormalities

There are many theories regarding the pathogenesis of venous ulcer. The oldest theories are venous stasis (Holmans [18]in 1917) and arteriovenous shunts (Pratt[19]in 1949, and Brewer[20]in1950). Homans suggested that hypoxia secondary to blood stasis was responsible for ulceration. Subsequent studies did not show hypoxia in the limb with ulcer.[21,22] The theory of arteriovenous shunts was strongly contested

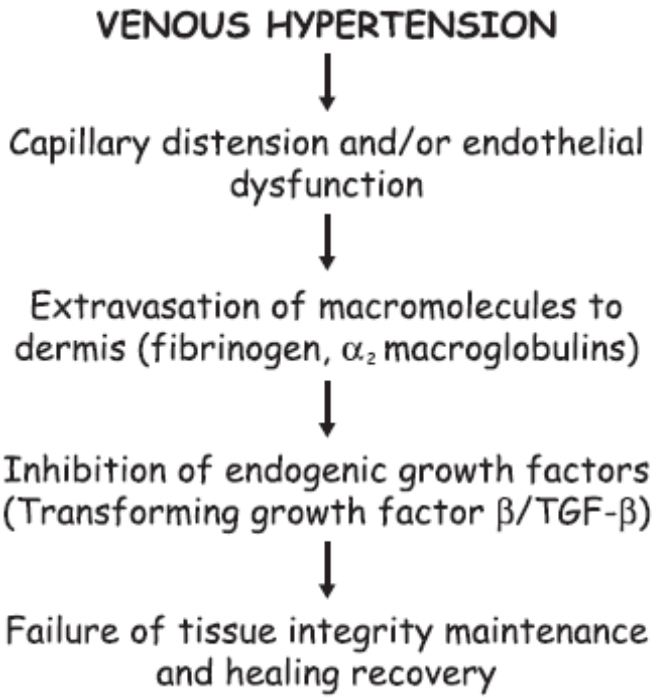
by findings of Lindemayr *et al*., who used radioactive microspheres and could not demonstrate shunts in patients with ulcer.[23] The more recent theories have associated CVI with microcirculatory abnormalities, with the generation of an inflammatory response. In 1982, Browse and Burnand suggested that venous hypertension in the calf muscular pump system is transmitted through the perforating/communicating system to the superficial veins of the skin and the subcutaneous tissue of the calf. [24] This increase in pressure would distend the local capillary bed and widen the endothelial pores, allowing large molecules, mainly fibrinogen, to escape into the interstitial fluid. Insoluble fibrin complexes form due to an inappropriate fibrinolytic activity in blood and interstitial fluid. Fibrin deposited around the capillary forms a barrier to oxygen and other nutrients, promoting cell death and ulceration (Fig. 1). However, Falanga and Eaglstein, in 1993, could not demonstrate that the fibrin cuffs were a real barrier to diffusion, observing that they were discontinuous around the capillaries and that the venous ulcers healed despite their presence on the ulcer border. [25]

In 1988, Coleridge Smith *et al*. proposed an alternative hypothesis to better explain venous ulcer pathogenesis. [26] According to these authors, increased pressure in the venous system, in the orthostatic position, leads to a pressure decrease of capillary perfusion, reducing the capillary flux sufficiently to cause leukocyte trap. The trapped leukocytes release toxic metabolites of oxygen and proteolytic enzymes which then cause capillary damage, making capillaries more permeable to large molecules and promoting additional leukocyte trap. The permeability

increase could result in extravasation of fibrinogen and other plasma proteins which would cause fibrin cuff formation. The trapped leukocytes would additionally damage the circulation of the affected capillaries, resulting in ischemic areas around the capillary loop (Fig. 3). This theory has been criticized because the studies were performed with patients whose cutaneous alterations were secondary to chronic venous hypertension. Therefore it is difficult to determine whether the leukocyte trap was causing the local inflammatory process or was secondary to it. In 1991, Claudy *et al* . proposed that activation of leukocytes released free radicals and proteolytic enzymes, and increased elastase activity, causing epithelial injury and increased vessel permeability, resulting in deposition of pericapillary fibrin.[27]Furthermore, these leukocytes would release tumor necrosis factor alpha (TNF-α), which decreases fibrinolytic activity, and secondarily induces the formation of pericapillary fibrin cuffs. Both fibrin and toxic metabolites released by leukocytes can explain the difficulties encountered in ulcer healing.

In 1993, Falanga *et al* . proposed that capillary distension or injury of endothelial cells due to venous hypertension leads to extravasation of fibrinogens, α2-macroglobulins and other macromolecules, from veins to dermis.[25]These macromolecules can cause a functional inhibition of endogenous growth factors, for instance transforming growth factor –β (TGF-β), making them unable to maintain tissue integrity and healing recovery (Fig. 3).

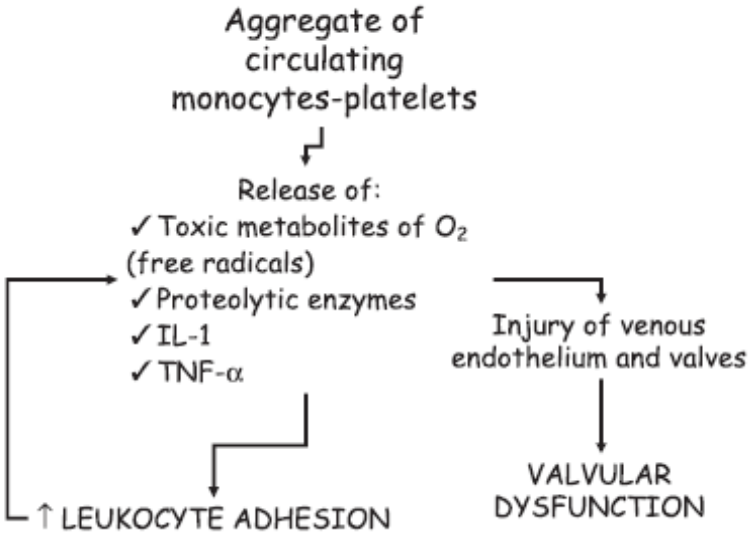
Fig.3 Scheme for the theory of Falanga and Eaglstein



There is evidence supporting this hypothesis. For example, there are growth factors abundantly present in venous ulcer, and some fluid collected from venous ulcers causes *in vitro* inhibition of proliferation of some types of important healing

cells, including fibroblasts, endothelial cells and keratinocytes. [28,29] Therefore, the microenvironment of venous ulcer is negative for these growth factors and makes healing difficult. The notion that venous ulcers contain a functional trap for growth factors would provide an explanation for unsuccessful single growth factor therapy, but it is difficult to explain how these events would cause inflammation and tissue death. The role of activated leukocytes in venous ulcer development has been studied. Monocytes are likely the leukocytes involved in many clinical stages in the development of CVI. [30] Besides activated monocytes, aggregates of monocytes–platelets have been recently implicated in CVI and venous ulcer etiopathogenesis. Peyton *et al* . were the first to show an increased number of these aggregates in patients with venous ulcer.[31]In 1999, Powell *et al* . showed an association of all classes of CVI with the increase of these circulating aggregate levels.[32] They also suggested that the circulating aggregate of monocytes– platelets would be able to injure the venous endothelium and valves, leading to the development of valvular dysfunction. The activated leukocytes release the substances mentioned above and the activated platelets release interleukin-1 (IL-1) and TNF-α, and both would act in endothelial cells to increase leukocyte adhesion (Fig. 4). However, the stimuli that activate monocytes and platelets are still unknown, as are the roles of these circulating aggregates. Activated monocytes as a cause of CVI are still the subject of investigation.

Fig. 4 Scheme for the theory of Powell et al.



In vivo microscopy studies have revealed areas of capillary microthrombosis in lipodermatosclerotic skin[33] and reductions in capillary numbers in areas of prior ulceration (atrophie blanche).[34] This suggests that cutaneous nutrient circulation may contribute to venous ulceration and recurrence. Despite the many studies that have been carried out and the various hypotheses that have been proposed, the real mechanism of CVI development and venous ulcer is still unknown. It is possible that each mechanism described above is important in some cases. Therefore, the etiopathogenesis of these diseases is still the subject of many current studies.

3.3.5 Risk factors

Heredity plays a significant role in the development of varicose veins. Moderate venous disease is independently related to age, previous hernia surgery, and

normotension in both sexes. In men, current walking, the absence of cardiovascular disease, and not moving after sitting are also predictive. Additional predictors in women are weight, number of births, oophorectomy, flat feet, and not sitting. For severe disease, age, family history of venous disease, waist circumference, and flat feet are predictive in both sexes. In men, occupation as a labourer, cigarette smoking, and normotension are also independently associated with severe venous disease. Additional significant and independent predictors in women are hours standing, history of leg injury, number of births, and cardiovascular disease, but African American ethnicity is protective.[35]

3.4 The C-E-A-P classification

This is a recent scoring system that stratifies venous disease based on *c*linical presentation, *e*tiology, *a*natomy, and *p*athophysiology. This classification scheme is useful in helping the physician coherently and thoughtfully assess a limb afflicted with venous insufficiency and then arrive at an appropriate treatment plan.

Classification of Chronic Lower Extremity Venous Disease

C	Clinical signs (grade$_{0–6}$, supplemented by “A” for asymptomatic and “S” for symptomatic presentation
E	Etiologic classification (*c*ongential, *p*rimary, *s*econdary)
A	Anatomic distribution (*s*uperficial, *d*eep, or *p*erforator, alone or in combination)
P	Pathophysiologic dysfunction (*r*eflux or *o*bstruction, alone or in combination)

CLINICAL CLASSIFICATION ($C_{0–6}$)

Any limb with possible chronic venous disease is first placed into one of seven clinical classes ($C_{0–6}$) according to the objective signs of disease.

Clinical Classification of Chronic Lower Extremity Venous Disease

Class 0	No visible or palpable signs of venous disease
Class 1	Telangiectasia, reticular veins, malleolar flare
Class 2	Varicose veins
Class 3	Edema without skin changes
Class 4	Skin changes ascribed to venous disease (e.g., pigmentation, venous eczema, lipodermatosclerosis)
Class 5	Skin changes as defined above with healed ulceration
Class 6	Skin changes as defined above with active ulceration

Limbs in higher categories have more severe signs of chronic venous disease and may have some or all of the findings defining a less severe clinical category. Each limb is further characterized as asymptomatic (A), for example, $C_{0–6,A}$, or symptomatic (S), for example, $C_{0–6,S}$. Symptoms that may be associated with telangiectatic, reticular, or varicose veins include lower extremity aching, pain, and skin irritation. Therapy may alter the clinical category of chronic venous disease. Limbs should therefore be reclassified after any form of medical or surgical treatment.

ETIOLOGIC CLASSIFICATION (E_C, E_P, or E_S)

Venous dysfunction may be congenital, primary, or secondary. These categories are mutually exclusive. Congenital venous disorders are present at birth but may not be recognized until later. The method of diagnosis of congenital abnormalities must be described. Primary venous dysfunction is defined as venous dysfunction of unknown cause but not of congenital origin. Secondary

venous dysfunction denotes an acquired condition resulting in chronic venous disease, for example, deep venous thrombosis.

Etiologic Classification of Chronic Lower Extremity Venous Disease

Congenital (E_C)	Cause of the chronic venous disease present since birth
Primary (E_P)	Chronic venous disease of undetermined cause
Secondary (E_S)	Chronic venous disease with an associated known cause (post-thrombotic, post-traumatic, other)

ANATOMIC CLASSIFICATION (A_S, A_D, or A_P)

The anatomic site(s) of the venous disease should be described as superficial (A_S), deep (A_D), or perforating (A_P) vein(s). One, two, or three systems may be involved in any combination. For reports requiring greater detail, the involvement of the superficial, deep, and perforating veins may be localized by use of the anatomic segments.

Segmental Localization of Chronic Lower Extremity Venous Disease

Segment No.	Vein(s)
SuperficialVeins ($A_{S1–5}$)	
1	Telangiectasia/reticular veins
	Greater (long) saphenous vein
2	*Above knee*
3	*Below knee*
4	Lesser (short) saphenous vein
5	Nonsaphenous
Deep Veins ($A_{D6–16}$)	

Segment No.	Vein(s)
6	Inferior vena cava
	Iliac
7	*Common*
8	*Internal*
9	*External*
10	Pelvic: gonadal, broad ligament
	Femoral
11	*Common*
12	*Deep*
13	*Superficial*
14	Popliteal
15	Tibial (anterior, posterior, or peroneal)
16	Muscular (gastrointestinal, soleal, other)
Perforating Veins ($A_{P17,18}$)	
17	Thigh
18	Calf

PATHOPHYSIOLOGIC CLASSIFICATION ($P_{R,O}$)

Clinical signs or symptoms of chronic venous disease result from reflux (P_r), obstruction (P_o), or both ($P_{r,o}$).

Pathophysiologic Classification of Chronic Lower Extremity Venous Disease

Reflux (P_R)

Obstruction (P_O)

Reflux and obstruction ($P_{R,O}$)

3.3.7 Clinical features

The patient with symptomatic varicose veins relates, most often, symptoms of aching, heaviness, discomfort, and sometimes outright pain in the calf of the affected limb. Many causes of leg pain are possible, and most may coexist. Therefore, defining the precise symptoms of venostasis is necessary. These symptoms may be of gradual onset or may be initiated by a lancinating pain, and they may precede the clinical appearance of the varicosity. Discomfort usually occurs during warm temperatures and after prolonged standing. Varicose vein symptoms are often disproportionate to the degree of pathologic change. Patients with small, early varices may complain more than those with large, chronic varicosities. The initial symptoms may vary from a pulsating pressure or burning sensation to a feeling of heaviness. The pain is characteristically dull, does not occur during recumbency or early in the morning, and is exacerbated in the afternoon, especially after long standing. This is particularly worse at the end of the day, most likely due to prolonged sitting or standing that results in venous distention and associated pain. The discomforts of aching, heaviness, fatigue, or burning pain are relieved by recumbency, leg elevation, or elastic support.

In the case of women, the symptoms are often most troubling and exacerbated during the menstrual period, particularly during the first day or two. It is not unusual for a patient to have significant reflux at the saphenofemoral junction and yet not have impressive varicose veins on physical examination. Additionally, the patient may have combined superficial and deep venous insufficiency, and thus a clear diagnosis, with the aid of the CEAP system, is useful in determining treatment.

Primary varicose veins consist of elongated, tortuous, superficial veins that are protuberant and contain incompetent valves. These produce the symptoms of mild swelling, heaviness, and easy fatigability. Primary varicose veins merge imperceptibly into more severe CVI. Swelling is moderate to severe, an increased sensation of heaviness occurs with larger varicosities, and early skin changes of mild pigmentation and subcutaneous induration appear. When CVI becomes severe, marked swelling and calf pain occur after standing, sitting, or walking. Multiple dilated veins are seen associated with various clusters and heavy medial and lateral supramalleolar pigmentation.

.Cutaneous itching is also a sign of venostasis and is often the hallmark of inadequate external support. It is a manifestation of local congestion and may precede the onset of dermatitis. This, and nearly all the symptoms of stasis disease, can be explained by the irritation of superficial nerve fibers by local pressure or accumulation of metabolic end products with a consequent pH shift. External hemorrhage may occur as superficial veins press on overlying skin within this protective envelope.

3.3.8 Complications

Chronic venous insufficiency can lead to hyperpigmentation, lipodermatosclerosis and superficial thrombophlebitis. There is an increased risk of cellulitis, leg ulceration, and delayed wound healing. Long-standing CVI also may lead to the development of lymphedema. Long standing ulcers can give rise to Marjolin's ulcer (squamous cell carcinoma).

3.3.9 Evaluation

The most important of all noninvasive tests available to study the venous system are the physical examination and a careful history that elucidates the symptoms mentioned earlier. Clinical examination of the patient determines the nature of the venostasis disease and ascertains the presence of intercutaneous venous blemishes and subcutaneous protuberant varicosities, the location of principal points of control or perforating veins that feed clusters of varicosities, the presence and location of ankle pigmentation and its extent, and the presence and severity of subcutaneous induration. After these facts have been obtained, the physician may turn to noninvasive techniques to corroborate the clinical impression. Visual examination can be supplemented by noting a downward-going impulse on coughing. Tapping the venous column of blood also demonstrates pressure transmission through the static column to incompetent distal veins.

The Perthes test for deep venous occlusion and the Brodie-Trendelenburg test of axial reflux have been replaced by in-office use of the continuous-wave, handheld Doppler instrument supplemented by duplex evaluation.[36] The handheld Doppler

instrument can confirm an impression of saphenous reflux, and this, in turn, dictates the operative procedure to be performed in a given patient. It is used in specific locations to determine incompetent valves. With distal augmentation of flow and release, with normal deep breathing, and with performance of a Valsalva maneuver, accurate identification of valve reflux is ascertained. Formerly, the Doppler examination was supplemented by other objective studies. These included the photoplethysmograph, the mercury stain-gauge plethysmograph, and the photorheograph. These are no longer in use. Another instrument reintroduced to assess physiologic function of the muscle pump and the venous valves is the air-displacement plethysmograph.[37] This instrument was discarded after its use in the 1960s because of its cumbersome nature. Computer technology has allowed its reintroduction as championed by Christopoulos and coworkers.[37] It consists of an air chamber that surrounds the leg from knee to ankle. During calibration, leg veins are emptied by leg elevation, and the patient is then asked to stand so that leg venous volume can be quantitated and the time for filling recorded. The filling rate is then expressed in milliliters per second, thus giving readings similar to those obtained with the mercury strain-gauge technique.

Duplex technology more precisely defines which veins are refluxing by imaging the superficial and deep veins. Valve closure requires a reversal of flow with a pressure gradient that is higher proximally than distally.[38] Thus, the duplex examination should be done with the patient standing or in the markedly trunk-elevated position.[39,40]

Imaging is obtained with a 10- or 7.5-MHz probe, and the pulsed Doppler consists of a 3.0-MHZ probe. The patient stands with the probe placed longitudinally on the groin. After imaging, sample volumes can be obtained from the femoral or saphenous vein. This flow can be observed during quiet respiration or by distal augmentation. Sudden release of augmentation allows assessment of valvular competence. The short saphenous vein and popliteal veins are similarly examined. Imaging improves the accuracy of the Doppler examination. Widespread use of duplex scanning has allowed a comparison of findings between standard clinical examinations with duplex Doppler studies.[41] In a study in which each patient was examined by three surgeons using different techniques (one using clinical examination, a second using the handheld Doppler instrument, and a third using a color duplex scanner), it was found that clinical examination failed in assessing main axial reflux at the saphenofemoral junction and saphenopopliteal junction. Whenever a Doppler instrument was added to the examination, the evaluation became more accurate. Based on preoperative assessments using clinical examination alone, inappropriate surgery would have been performed in 20% of the limbs. Clinical examination plus Doppler study would have produced a 13% incidence of inappropriate surgery.

Phlebography

In general, phlebography is unnecessary in diagnosis and treatment of primary venostasis disease and varicose veins. In the complex problems of severe CVI,

phlebography has specific utility. Ascending phlebography defines obstruction. Descending phlebography identifies specific valvular incompetence suspected on B-mode scanning and clinical examination.

3.3.10 Treatment options

Nonoperative management includes avoidance of prolonged standing or sitting, use of elastocrepe bandage or stockings, elevation of lower limbs and compression therapy. Recently some drugs e.g., microflavanoids have also been used.

The standard surgical treatment is Trendelenburg's operation, stripping of great saphenous vein and multiple stab avulsions of perforators. Subfascial endoscopic perforator ligation, endovenous laser therapy, radiofrequency ablation, transilluminated power phlebectomy and foam sclerotherapy are other modalities of treatment.

3.4 Venous ulcer[42]

Venous ulcers constitute approximately 80% of all leg ulcers. Venous leg ulcers have been estimated to afflict 0.2% to 1% of the total population and 1% to 3% of the elderly.[43]

3.4.1 Diagnosis of lower extremity ulcers

Gross arterial disease should be ruled out by establishing that pedal pulses are present on physical examination and/or that the ankle : brachial index (ABI) is > 0.8. (Any ABI less than 1.0 suggests a degree of vascular disease and compression therapy is usually considered to be contraindicated with an ABI < 0.7.) In elderly patients, patients with diabetes mellitus, or patients with an ABI > 1.2, a toe: brachial index of > 0.6 or a trans-cutaneous oxygen partial pressure of > 30mmHg in the region of the ulcer may help to suggest an adequate arterial flow.

Color duplex ultrasound scanning performed with proximal compression or a Valsalva maneuver is useful in providing anatomic and physiologic data helping to confirm a venous etiology for the leg ulcer. Patients presenting with an apparent venous ulcer and who are suspected of having sickle cell disease should have a sickle cell prep and a hemoglobin electrophoresis. Apparent venous ulcers that have been open continuously without signs of healing for 3 months or that do not demonstrate any response to treatment after 6 weeks should be biopsied for histological diagnosis.[44] This is to rule out malignancy, vasculitis, collagen-vascular diseases, and dermal manifestations of systemic diseases.

Apparent venous ulcers, as well as all wounds, that are excessively painful and that progressively increase in size after debridement and/or despite treatment should be considered for other diagnoses such as pyoderma gangrenosum, IgA

monoclonal gammopathies, Wegener's granulomatosis, cutaneous chronic granulomatous disease, and mycobacterial or fungal etiologies. This suspicion should be especially high if the ulcer is darker in color, has blue/purple borders, or if the patient has a systemic disease such as Crohn's disease, ulcerative colitis, rheumatoid arthritis, collagen vascular diseases, leukemia, or immunosuppression.

3.4.2 Lower extremity compression

The use of a Class 3 (most supportive) high-compression system (three layer, four layer, short stretch, paste-containing bandages, e.g., Unna's boot, Duke boot) is indicated in the treatment of venous ulcers. Although these modalities are similar in effectiveness, they can differ significantly in comfort and cost. The degree of compression must be modified when mixed venous/arterial disease is confirmed during the diagnostic work-up. Intermittent pneumatic pressure (IPC) can be used with or without compression dressings and can provide another option in patients who cannot or will not use an adequate compression dressing system.

3.4.3 Infection control

Infection results when the bacteria: host defense equilibrium is upset in favor of the bacteria. Infection plays various roles in the etiology, healing, operative repair, and complications of venous ulcers. Remove all necrotic or devitalized tissue by sharp, enzymatic, mechanical, biological, or autolytic debridement. If infection is

suspected in a debrided ulcer, or if epithelialization from the margin is not progressing within 2 weeks of debridement and initiation of compression therapy, determine the type and level of infection in the debrided ulcer by tissue biopsy or by a validated quantitative swab technique.[45] For ulcers with >/=1x10^6 CFU/g of tissue or any tissue level of beta hemolytic streptococci following adequate debridement, decrease the bacterial level with topical antimicrobial therapy. Once in bacterial balance, discontinue the use of the topical antimicrobial agent to minimize any possible cytotoxic effects due to the antimicrobial agent or emergence of bacterial resistance to the agent. Cellulitis surrounding the venous ulcer should be treated with systemic gram-positive bactericidal antibiotics.

3.4.4 Wound bed preparation

Wound bed preparation is defined as the management of the wound to accelerate endogenous healing or to facilitate the effectiveness of other therapeutic measures.

The aim of wound bed preparation is to convert the molecular and cellular environment of a chronic wound to that of an acute healing wound.

Examination of the patient as a whole is important to evaluate and correct causes of tissue damage. This includes factors such as: systemic diseases and medications, nutrition, and tissue perfusion and oxygenation.

Initial debridement is required to remove the obvious necrotic tissue, excessive bacterial burden, and cellular burden of dead and senescent cells. Maintenance

debridement is needed to maintain the appearance and readiness of the wound bed for healing. The health care provider can choose from a number of debridement methods including sharp, enzymatic, mechanical, biological, or autolytic. More than one debridement method may be appropriate. Wounds should be cleansed initially and at each dressing change using a neutral, nonirritating, nontoxic solution. Routine wound cleansing should be accomplished with a minimum of chemical and/or mechanical trauma.

3.4.5 Dressings

There is a plethora of choices for topical treatment of venous ulcers. Many dressings now combine wound bed preparation, i.e., debridement and/or antimicrobial activity, with moisture control. Guidelines are necessary to help the clinician make decisions regarding the value and best use of these advanced wound care products. Most dressings will be used in combination with compression systems.

Use a dressing that will maintain a moist wound-healing environment. Continuously moist saline gauze dressings are as effective as other types of moist wound healing in terms of healing rate, although they may have other drawbacks such as maceration of the peri-ulcer skin, practicality of use, and cost effectiveness. The use of compression systems for venous ulcers alleviates the need for adhesive to keep the primary dressing in place. However, additional tissue damage may result if the dressing causes increased pressure on the wound

or damages adjacent tissue. Venous ulcer patients are particularly susceptible to contact dermatitis related to topical therapies. Because of their low unit cost, moist saline gauze dressings are often viewed as the least expensive and, therefore, most cost-effective dressing. Emerging therapies through recombinant technologies and cell-based devices may offer benefit and increase healing in selected patients or difficult wounds.

3.4.6 Surgery in venous ulcer

The mainstay of moist wound dressings and a compression system are not successful in healing all venous ulcers. Also, they do not fully address the etiology of increased ambulatory venous pressure. Over the years, multiple surgical procedures have been attempted to treat venous ulcers with varying degrees of success. True randomized clinical trials comparing operative techniques are rare in the literature, but data are available supporting surgery in selected patients.

Skin grafting of a venous ulcer, without attention to the underlying venous disease, is not a long-term solution and is prone to recurrent leg. Trendelenburg's operation along with stripping of great saphenous vein and stab avulsions of perforators is the standard procedure. Subfascial endoscopic perforator surgery (SEPS) can also be combined with Trendelenburg's operation. The procedure is not effective if the patient has severe deep venous disease with either deep reflux or obstruction.

Less extensive surgery on the venous system such as superficial venous ablation, endovenous laser ablation, or valvuloplasty, especially when combined with compression therapy, can be useful in decreasing the recurrence of venous ulcers. Free flap transfer with microvascular anastomoses can benefit recalcitrant venous ulcers with severe lipodermatosclerosis by allowing wide excision of diseased tissue and providing uninjured venous valves in the transferred tissue.[46]

3.4.7 Use of adjuvant agents (topical, device and systemic)

Cytokine growth factors have yet to be shown to demonstrate sufficient statistically significant results of effectiveness to recommend any of them for treatment of venous ulcers, although isolated reports suggest their potential usefulness. There is evidence that a bilayered artificial skin (biologically active dressing), used in conjunction with compression bandaging, increases the chance of healing a venous ulcer compared with compression and a simple dressing. Cultured epithelial autografts or allografts have not been demonstrated to improve stable healing of venous ulcers. Electrical stimulation may be useful in reducing the size of venous leg ulcers.[47] Negative pressure wound therapy may be useful prior to a skin graft/flap by helping promote the development of granulation tissue in the wound base, or postoperatively by preventing shearing and removing exudates. However, its reported experience in venous ulcers is limited.[48] Laser therapy, phototherapy, and ultrasound therapy have not been shown statistically to improve venous ulcer healing. Sclerotherapy may be useful as an adjunct to compression therapy in the treatment of venous ulcers. [49]

Pentoxifylline used in conjunction with compression therapy improves healing of venous ulcers by improving microcirculation. The role of eicosanoids (prostaglandins) or prostaglandin antagonists in the treatment of venous ulcers lacks sufficient data to allow a recommendation. Oral treatment with micronized purified flavonoid fraction (MPFF) may be a useful adjunct to conventional compression therapy in the treatment of leg ulcers.[50] These agents inhibit the synthesis of free oxygen radicals, decrease microvascular leakage, and inhibit leukocyte trapping and activation. Fibrinolytic enhancement with an anabolic steroid such as stanozolol in conjunction with compression therapy may be useful in treating lipodermatosclerosis associated with venous ulcers. However, one must be aware of side effects. Oral zinc supplementation is not useful in the treatment of venous leg ulcers.

3.5 Foam Sclerotherapy

3.5.1 Sclerotherapy

Sclerotherapy is the targeted elimination of intracutaneous, subcutaneous, and/or transfascial varicose veins (perforating veins) as well as the sclerosation of subfascial varicose vessels in the case of venous malformation by the injection of a sclerosant. The various sclerosants provoke a marked damage of the endothelium of the vessels and possibly of the entire vascular wall. Subsequently, a secondary, wallattached local thrombus is generated, and in the longterm, the veins will be transformed into a fibrous cord, that is, sclerosis[51]. The purpose of sclerotherapy is not just a thrombosis of the vessel, which, per se, is subject to recanalization, but

the definite transformation into a fibrous cord. This cannot recanalize and corresponds to the surgical removal of a varicose vein as far as the functional result is concerned.

3.5.2 Sclerosing foam

This is a nonequilibrium dispersion of gas bubbles in a sclerosing solution, where the sclerosing solution contains surface-active molecules, where the gas is physiologically tolerated at therapeutic doses, and where the gas fraction is equal to or greater than 0.52. Sclerosing foam is characterized by (at least) the following variables: type and concentration of the tensioactive sclerosing agent, type of gas, ratio of liquid to gas, the method of preparation, the time between processing and use, and bubble sizes. The behavior of sclerosing foam is quite different compared to the action and the properties of liquid sclerosing solutions[52].

3.5.3 Foam vs liquid sclerotherapy

Foam sclerotherapy holds several advantages over traditional liquid sclerotherapy. Once a liquid is injected, it mixes with the blood in the vein, and the concentration of the sclerosant is diluted. Foam, on the other hand, displaces the blood, allowing direct contact of the sclerosant with the endothelium. The efficacy of a given concentration of sclerosant is effectively increased when used as foam instead of liquid. Accordingly, we can use a lower concentration of a given sclerosant to treat veins. This increases the safety of sclerotherapy. Greater safety is also achieved

with foam for other reasons. A given volume of liquid can be used to produce 4 or 5 times its volume in foam, depending on the foaming method. This allows the use of lower total dose of the sclerosant to achieve the desired effect. Moreover, extravasated foam is much better tolerated than extravasated liquid. The air contained in the foam is echogenic. This dramatically increases visibility and accuracy when performing duplex-guided sclerotherapy.

Besides being composed of different specific ingredients, foams can differ in compactness, durability, and density. Compactness is related to the size of the air bubbles. Macrofoam contains bubbles larger than 500 μm; minifoam contains bubbles between 250 and 500 μm; and microfoam is composed of bubbles smaller than 250 μm. Since smaller bubbles ensure better contact with the endothelium for most therapeutic purposes, most experts would prefer microfoam, and most methods of foam production would strive to achieve this standard.

3.5.4 Pathophysiology

After sclerotherapy the pathologic damage is immediate. After only 2 minutes of foam drug exposure, the endothelial and part of tunica media are seriously damaged and after a few minutes the detachment of the endothelial epithelium. The sclerosis developed after only 30 minutes with

the presence of a microthrombus. In only 30 minutes with the foam sclerotherapy, the same result is obtained that which is obtained in almost 2 to 3 hours by the liquid sclerotherapy[53]. In our report, there is no histologic difference among the six

patients. The endothelial damage was synchronous: necrosis, endothelial detachment, and early sclerosis developed from the vein wall[54].

3.5.5 Safety of foam

The stress that foam places on the human respiratory system is still unclear, although complications rates are exceedingly low. Frullini and Cavezzi proposed a limit of 3 mL of foam per each session of sclerotherapy, although no major complications such as pulmonary embolism, deep vein thrombosis, ischemic lesions, or anaphylactic reaction were recorded. Others suggest less than 10 mL, while some routinely use up to 40 mL without serious sequelae. However, when larger doses are used, there are incidents of dry cough, chest discomfort, transient ischemic attacks, and scotomas.

Of note, Cabrera et al used up to 80 mL without respiratory or neurologic complications. The decision to use such large volumes may rely on the use of carbon dioxide instead of room air. Carbon dioxide has much higher solubility than nitrogen, the primary component of room air. However, no publication to date has compared the effect of different gases.

Although sterile gas may be preferred from a medical-legal standpoint, in everyday practice the use of filtered air seems unnecessary. Frullini points out that while operating-room air is not sterile, surgeons commonly expose the interior of a patient for hours during major operations.

In a prospective study of large-volume foam sclerotherapy for venous insufficiency, no deep vein thrombosis was detected in patients experiencing leg pain or swelling after the procedure. But since deep vein thrombosis can be clinically silent, some may have been missed.

Studies have revealed that a precapillary arteriovenous shunt might allow a direct flow of sclerosant from the venous to the arterial circulation. Therefore, even with expert technique using a conservative sclerosant dose and concentration, cutaneous ulcerations may occur.

Mason et al examined the coagulation status of patients with vascular anomalies who had undergone sclerotherapy or embolization by measuring fibrinogen, platelet, D-dimer levels, and prothrombin time for 29 patients before and after treatment. The researchers concluded that patients who received dehydrated alcohol or sodium tetradecyl sulfate sclerotherapy might experience coagulation abnormalities that put them at increased risk for bleeding, thrombosis, or hematoma. Similar studies have not been done for foam sclerotherapy of venous malformations.

3.5.6 Indications

The objectives of sclerotherapy are:

- Treatment of varicosis and prevention of possible complications
- Reduction or elimination of existing symptoms
- Improvement of pathologically altered hemodynamics and

- Achievement of a good result that satisfies aesthetic and functional criteria.[55]

In principle all vein calibers are suitable for foam sclerotherapy. Foam gives a better outcome in larger vein calibers (C2 varicose veins) and recurrent varicose veins (compared to conventional sclerotherapy). Some published data show good results in venous malformations. The larger the diameter of the vein, the more viscous the foam should be to obtain better results. The smaller the diameter of the vein the more liquid the foam should be for easier injection and to reduce possible tissue damage. With viscous foams a lower caliber threshold exists. Below that, vein-size viscous foams could cause more tissue damage.

Possible New Indications for Foam Sclerotherapy[56,57]

- Interventional angioradiologic procedures
- Pelvic congestion syndrome
- Varicocele
- Hydrocele
- Angiodysplasia
- Metastatic lesions
- Vascular malignant tumors
- Baker's cyst
- Hemorrhoids[58]

3.5.7 Contraindications

Absolute contraindications are:

- Known allergy to the sclerosant
- Severe systemic disease
- Acute superficial or deep vein thrombosis
- Local infection in the area of sclerotherapy or severe generalized infection
- Immobility
- Confinement to bed
- Advanced peripheral arterial occlusive disease
- Hyperthyroidism (in the case of sclerosants containing iodine) and
- Pregnancy in the first trimester and after the 36th week of gestation.

Relative contraindications are:

- Leg edema
- Late complications in diabetes (e.g., polyneuropathy)
- Mild peripheral arterial occlusive disease
- Poor general health
- Bronchial asthma
- Marked allergic diathesis

- Known hypercoagulability and
- Thrombophilia with history of deep vein thrombosis
- Patent foramen ovale

3.5.8 Complications and Risks

If performed properly, sclerotherapy is an efficient treatment method with a low incidence of complications. Nevertheless, a series of adverse events may occur in the context of the therapy.

Categorization of Sclerotherapy Complications[59]

Frequent, transient

Telangiectatic matting (10–30%)

Postsclerotherapy pigmentation (10–30%)

Pain with injection

Urtication post-injection (worse with polidocanol) [60]

Rare, self-limited

Cutaneous necrosis [61]

Superficial thrombophlebitis

Nerve damage (saphenous, sural) [62]

Transient visual disturbances, especially in migraine patients,

Hematuria

Rare, major

Anaphylaxis

Deep vein thrombosis, pulmonary embolism

Early reaction type allergy up to anaphylactic shock as well as an inadvertent intraarterial injection are very rare complications constituting an emergency situation. Skin necroses are described after paravascular injection of sclerosants in higher concentrations as well as, but rarely, after properly performed intravascular injection with various sclerosants, for example, 0.5% polidocanol in the treatment of spider veins.

In the second case, a mechanism involving transition of the sclerosant via arteriovenous anastomoses into arterial vessels has been discussed. In individual cases, this was described as embolia cutis medicamentosa.

Hyperpigmentations are described with a frequency of 0.3% to 10%. In general, they regress slowly. Matting, fine telangiectasias in the area of a sclerosed vein, is an unpredictable individual reaction of the patient and can also occur after surgical removal of a varicose vein.

Nerve damage has been described experimentally after paravascular injection. Further transitory appearances after sclerotherapy are intravascular clots, phlebitis, and hematomas. Additionally, complications may arise from the compressive bandage such as, for example, formation of blisters.

Intravascular clots can be squeezed out after stab incision to reduce the development of hyperpigmentation. Sclerotherapy is an intervention that requires patient information.

With large (20 mL) or very large amounts (33 mL and more) [63, 64] deep venous thromboses have been reported. For liquid foams prepared from diluted liquid sclerosing solutions, there is probably a higher incidence of visual disturbance and migraine in patients predisposed to these conditions.[65]

3.5.9 Diagnostics before Sclerotherapy

Diagnostic evaluation includes study of the medical history, clinical examination, and Doppler ultrasonography. Additionally, functional examinations (e.g., photoplethysmography, phlebodynamometry, venous occlusion plethysmography) and imaging (e.g., duplex ultrasonography, phlebography) can be taken into consideration. Functional examinations make it possible to assess the improvement of venous function, which is to be expected for the elimination of varicosis. Diagnostic imaging is especially suited for the identification of incompetent communications with the deep venous system, diagnostic clarification of postthrombotic alterations, and the assessment of a combined surgical treatment that may have to be performed.[66]

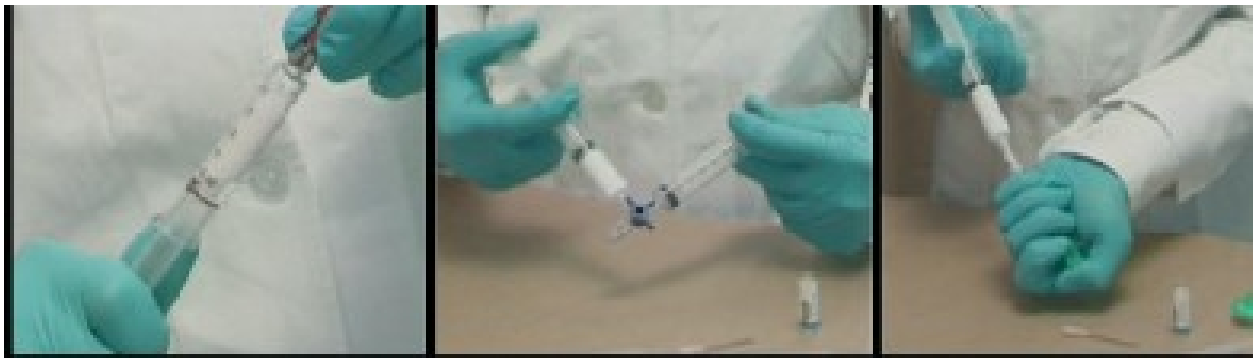
3.5.10 Methods for the Preparation of Extemporary Foam

i) The Monfreux method

Sclerosing foam is generated using a glass syringe that contains liquid sclerosing solution. The outlet of the syringe is sealed by a rubber or plastic cap.

Pulling back the piston generates a subatmospheric pressure, drawing air into the syringe through the gap between the syringe body and the piston. A rather fluid foam with fairly large bubbles is generated. [67]

Figure 4. Methods for the preparation of extemporary foam. Left,
Monfreux technique; middle, Tessari technique; right, double-syringe technique.



ii) The Tessari technique

Sclerosing foam is generated with two disposable plastic syringes. One syringe contains the liquid sclerosing solution, and the other contains air. The outlets of the syringes are connected with a three-way tap or a two-way-connector. Pumping the contents of both syringes backward and forward (approximately 20 times for the original Tessari technique (also known as Tourbillion technique) or 5 times with additional pressure and 7 times without additional pressure for the DSS technique, a variation of the basic technique by Tessari) causes a turbulent flow that generates foam. The liquid-to-air ratio varies from 1:4 (one plus three) to 1:5

(one plus four) for the original Tessari technique. Tessari's technique gives small-bubbled foam, which is rather fluid if low concentrations of sclerosants are used or viscous if high concentrations of sclerosants are used. Foam properties vary with the concentration of the liquid sclerosing solution, the types of syringes, and the mode of pumping.[68]

iii)The double-syringe system (DSS) technique

The double-syringe system version is defined for 3% polidocanol solution, two latex-free 10-mL syringes (one with rubber plunger) and a fixed liquid-to-air ratio of exactly 1:5 (one plus four). Pumping the contents of both syringes backward, 5 times with additional pressure or 7 times without additional pressure, generates foam. This procedure gives small-bubbled viscous foam.

3.5.11 Procedure

Foam is injected into the vein to be obliterated under ultrasound guidance, either directly or via an intravenous catheter. Usually this is done proximal to distally, though the other way is also equally acceptable. There should be a minimum distance of 10 cm from sapheno-femoral junction to the point of injection. The limb should be elevated once the foam has been injected. The foam can be manipulated using the probe to wherever it is needed. Once the foam reaches the sapheno femoral junction, compression is given using the probe for 10 minutes. Then deep veins are screened for any foam particle and if present, they are washed off by alternative flexion-extension at ankle joint. Elastocrepe bandage or stockings is applied and the patient is asked to walk for atleast 30 minutes. This is

to improve deep venous circulation to wash away any foam that has entered the deep system.

4.0 Materials and methods

4.1 Sample size and randomisation

Since there were no previous similar studies, it was planned to arbitrarily include 60 patients and randomly allocate 30 patients each to surgery and foam sclerotherapy group.

4.2 Inclusion criteria

All patients with symptomatic primary venous insufficiency of lower limbs, who were willing for definitive management with surgery and foam sclerotherapy, were included.

4.3 Exclusion criteria:

- Patients with a history or duplex finding of deep venous thrombosis
- Patients who had already undergone surgery for superficial venous insufficiency
- Patients not willing for randomization

4.4 Informed consent

All the patients were explained about their disease and treatment options available. The complications and long term results of both the procedures were explained. Only those patients who were willing for random allocation to either surgery or foam sclerotherapy were included in the study. Patients were free to withdraw from the study at any time.

4.5 Methodology

All patients presenting with features of venous insufficiency underwent clinical examination and venous duplex examination. Patients who were willing for definitive management were randomized into two groups – one for surgery and another for foam sclerotherapy.

4.6 Conventional Surgery

Trendelenburg's operation, stripping of great saphenous vein, stab avulsion of pre-marked varicose veins with or without sapheno-popliteal junction ligation were done.

Postoperative pain was assessed with visual analog scoring system and analgesic requirement. Postoperative complications were noted.

Elastocrepebandage was applied continuosly for 3 days and during daytime for 6 weeks postoperatively.

Clinical assessment and duplex screening for recurrence was done at 3 months. Assessment was done using CEAP class and venous severity score.

4.7 Ultrasound guided foam sclerotherapy

4.7.1 Technique of foam production (Tessari method)

Foam was prepared using two 10 ml syringes and a three way stop cock. 2 ml of 3% Sodium tetra decyl sulphate and 8 ml of air were taken and about 20 passes were made between the two syringes. The stability of foam thus obtained was 2-3 minutes.

4.7.2 Procedure

1) Venous network was mapped and drawn on skin and site of injection was chosen usually 10 cm below the knee.
2) A 24 gauge intravenous catheter was placed under ultrasound guidance into the vein to be obliterated.
3) Intravenous position is confirmed
4) Foam was prepared using Tessari method
5) Foam injected under ultrasound guidance and massaged with probe in the varicose network.
6) Sapheno-femoral junction was compresses with probe for 10 minutes when foam reached there.
7) Deep veins screened for foam; if present, cleared with rapid ankle flexion and extension maneuvers.

8) Elastocrepebandage or grade 2 compression stockings applied for 3 days continuously and then during daytime only for 6 weeks.
9) Walking for 30 minutes immediate post procedure and daily.
10) Severity of pain and complications were noted.
11) Surveillance with duplex examination was done at 1 week and injection done if necessary.
12) After 3 months, clinical examination, duplex study and assessment of symptoms were done.

4.8 Statistical Analysis

The results were tabulated on a spread sheet and statistical analysis was done using SPSS software with the help of bio-statistician.

5.0 Results

5.1 Improvement in CEAP class

Group	Parameter	At Presentation	At 3 months
Surgery	Mean	4.30	3.00
	Standard deviation	1.264	1.819
Foam Sclerotherapy	Mean	4.23	2.62
	Standard deviation	1.382	1.781

In the surgery group the mean CEAP class improved from 4.3 to 3.0. In the foam sclerotherapy group the mean CEAP class improved from 4.23 to 2.62. Using Mann-Whitney test, there was no statistically significant difference between the improvements seen in both the groups (p=0.235).

5.2 Improvement in Venous Severity Score (VSS)

Group	Parameter	At Presentation	At 3 months
Surgery	Mean	5.57	2.30
	Standard deviation	3.730	2.409

Foam Sclerotherapy	Mean	5.40	1.67
	Standard deviation	3.379	1.516

In the surgery group the mean VSS improved from 5.57 to 2.3. In the foam sclerotherapy group the mean VSS improved from 5.4 to 1.67. Using Mann-Whitney test, there was no statistically significant difference between the improvements seen in both the groups (p=0.381).

5.3 Symptomatic Improvement

In the surgery group 29 out of 30 patients i.e., 96.7% had symptomatic improvement compared to 28 out of 30 patients i.e., 93.3% in sclerotherapy group. There is no statistical difference in the symptomatic improvement between the two groups (p=0.47).

5.4 Complications

Surgery

- Wound infection – 2
- Wound dehiscence – 1
- Bruising – 1

Foam sclerotherapy

- Skin necrosis – 1
- Phlebitis – 2
- Staining – 1

Complications in both the groups were minor and rates were similar.

5.5 Analgesic requirements

- Surgery:
  - All patients required oral analgesics. In addition, 60% required injectable analgesic.
- UGS:
  - Only 20% of patients in foam sclerotherapy required any analgesic.

5.6 Cost of procedure

- Surgery: Approximately, Rs. 10,000
- UGS: Approximately, Rs. 1,500

5.7 Time to return to work

- Surgery: Average 7 days
- UGS: Average < 1 day

5.8 Number of injections required for foam sclerotherapy

- 85% Single injection
- 15% Two injections

5.9 Time required to do the procedure

- 15 to 20 minutes for each sitting of sclerotherapy
- 45 to 75 minutes for surgery

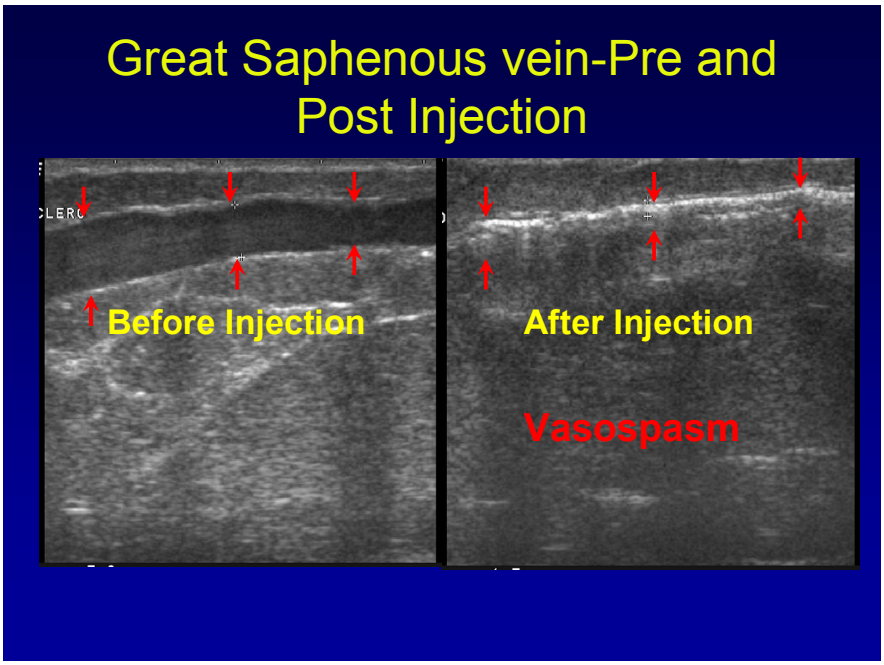
6.0 Pictures

6.1 Preparing foam by Tessari method

6.2 Puncturing great saphenous vein under ultrasound guidance

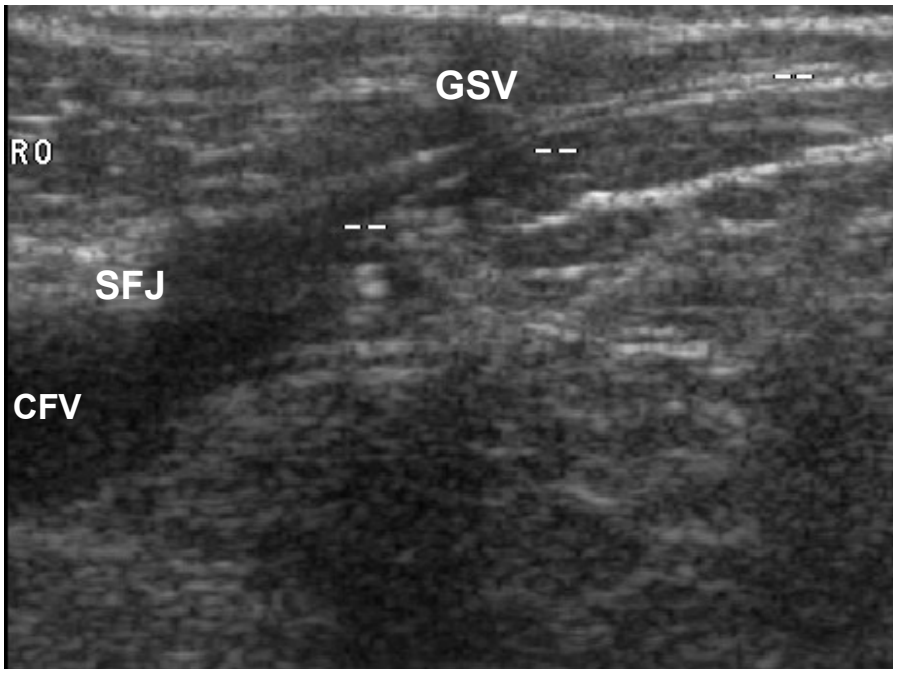
6.3 Injection of foam into great saphenous vein

6.4 Venospasm after injection of foam

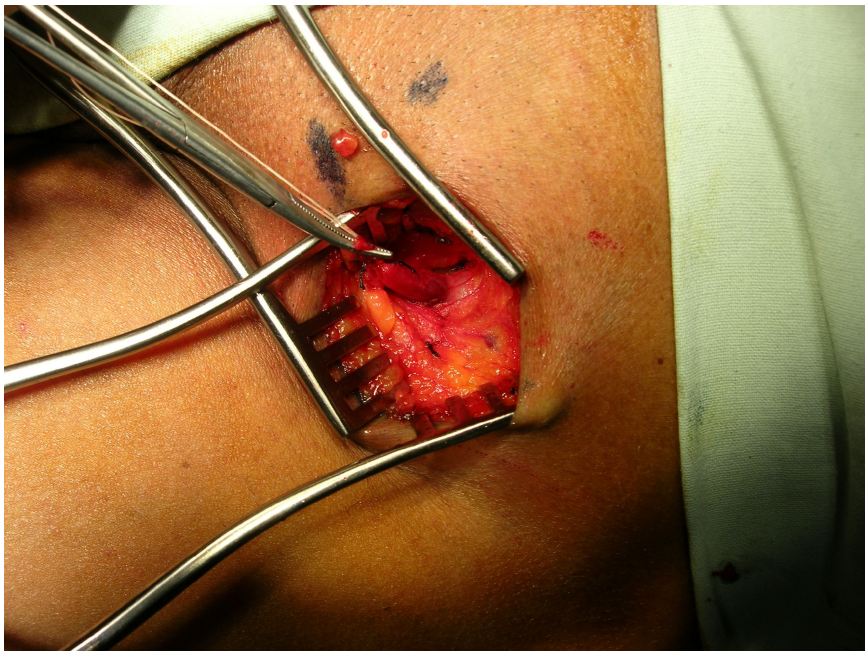


6.5 Compression at the sapheno-femoral junction

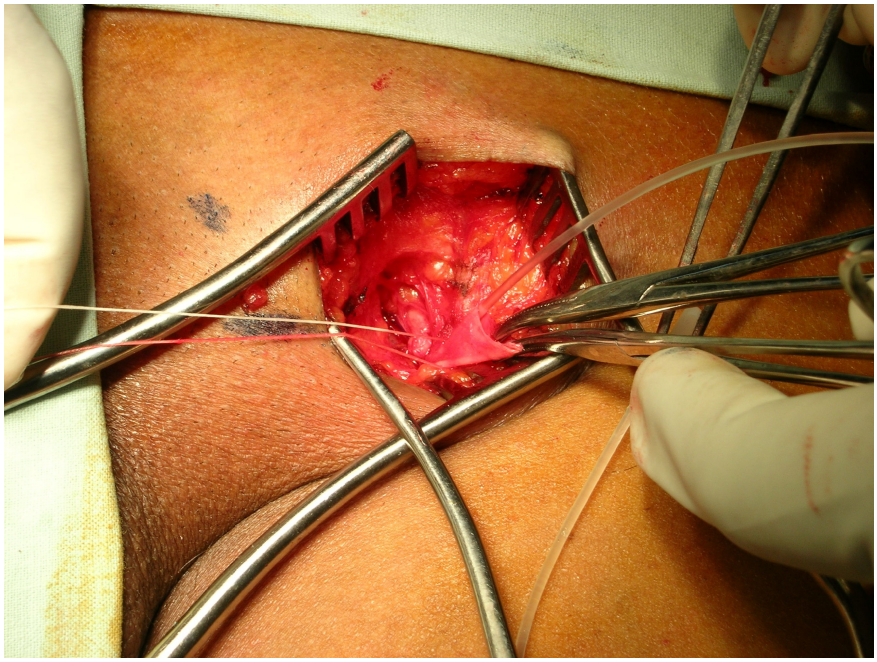
6.6 Sapheno-femoral junction at 3 months



6.7 Exposure of sapheno-femoral junction



6.8 Cannulating great saphenous vein prior to stripping

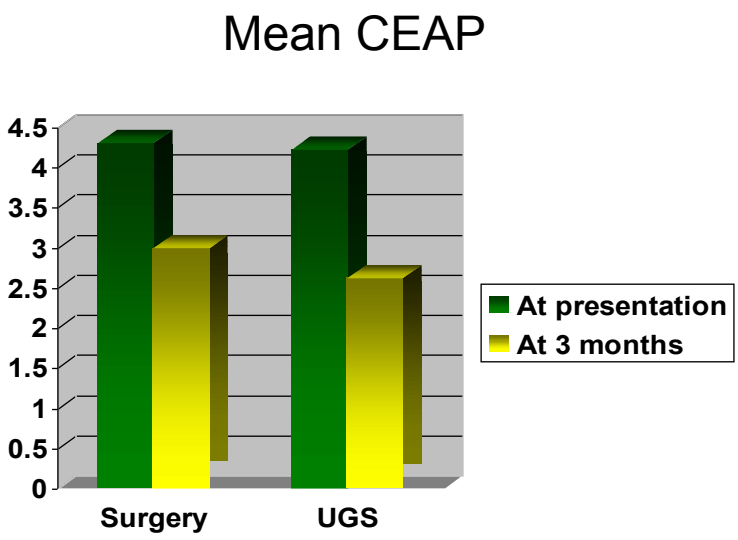


6.9 Applying Esmarch bandage to reduce blood loss

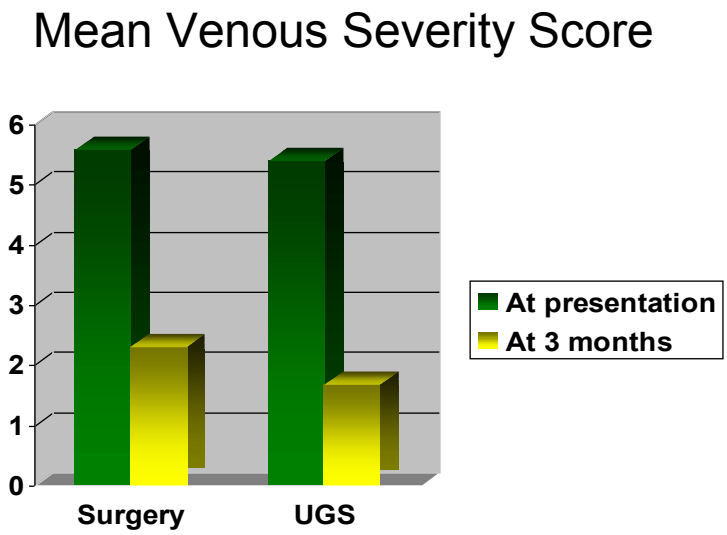
6.10 Multiple stab avulsions of varicose veins

7.0 Graphs

7.1 Mean CEAP class at presentation and 3 months



7.2 Mean Venous Severity Score at presentation and 3 months



8.0 Discussion

Despite the high prevalence of chronic venous insufficiency, they are often neglected or inadequately managed. Though surgery has been the gold standard of treatment, it has not been able to achieve complete cure in all the patients. In the quest to find better treatments with lesser morbidity, many newer modalities have come into vogue. Of all these foam sclerotherapy has shown promising results. It is safe, easy to perform and cheap, making it ideal for a developing country like ours.

The pre-procedure epidemiological characteristics, CEAP class and venous severity score were similar in both the groups. There was no recanalisation of

superficial system at 3 months in both the groups, proving the efficacy of foam sclerotherapy in the short term. The improvement in CEAP class and venous severity scores was comparable in both the groups. D.G. Bountouroglou et al[13], Bergan et al [69], Pascarella et al [71] and Guex[75] have reported similar improvements in their study.

The number of injections required to obliterate great saphenous vein was one in 85% of the patients. The remaining 15% required a second injection.

A recent systematic review of foam sclerotherapy for varicose veins by Jia et al has concluded that there is insufficient evidence to allow a meaningful comparison of the effectiveness of this treatment with that of other minimally invasive therapies or surgery. But the meta-analysis for complete occlusion suggests that foam sclerotherapy is less effective than surgery (relative risk - 0.86). [72]

From our study we conclude that foam sclerotherapy can be considered a good alternative for surgery in terms of its efficacy in short term.

The complications that occurred in foam sclerotherapy were mostly in the early part. One patient developed skin necrosis due to accidental extravasation. As the learning curve improved the complications decreased. Our complication rate was about 10%; there was no serious adverse event. The complication rates reported by other investigators were also low.[69,73,74] In a series of 6,395 injections with foam by Guex et al, the adverse events reported were less than 0.4%.[75] In the systematic review by Jia et al[72], the median rates of serious adverse events,

including pulmonary embolism and deep vein thrombosis, were less than 1 per cent. The median rate of visual disturbance was 1.4 per cent, headache 4.2 per cent, thrombophlebitis 4.7 per cent, matting/skin staining/pigmentation 17.8 per cent and pain at the site of injection 25.6 per cent.[72]

Most of the patients undergoing foam sclerotherapy were able to continue working on the same day when compared to surgery group in which 2 to 3 days hospitalization and 3 to 5 days of leave from duty were needed. This definitely proves the minimal morbidity and patient friendliness of foam sclerotherapy. Bergan et al also reported no disability down time in their initial experience of 322 patients.[69] Wright et al reported the time to return to work as ranging from 1 to 6 weeks following surgery for varicose veins.[70] In a randomized controlled trial by D.G. Bountouroglou et al, the median time to return to normal activities was significantly reduced in the foam sclerotherapy group (2 days) compared to the surgical group (8 days)[13] The median time of 2 days reported in this study was due to the addition of saphenofemoral ligation to foam sclerotherapy.

Foam sclerotherapy was about 6 times cheaper than surgery in our study. The overall cost of the procedure in the sclerotherapy group (£672.97) was significantly less compared to conventional surgery (£1120.64) in a study by D.G. Bountouroglou et al.[13] In this study, foam sclerotherapy was combined with saphenofemoral ligation which may have increased the cost of procedure.

The time required to do the procedure was also considerably shorter than surgery. It usually takes 15 to 20 minutes each session of foam sclerotherapy while surgery usually requires 45 to 75 minutes. In a similar study, the time taken to complete treatment was shorter in the foam sclerotherapy plus SFJ ligation group compared to conventional surgery: 45 *vs*. 85 min.[13]

Moreover foam sclerotherapy is an outpatient procedure with no need for anaesthesia, thus reducing the burden of health care.

We acknowledge that a small threat to validity (i.e., a bias) may exist in this study since the investigators were not blinded.

9.0 Conclusions

1. Obliteration of superficial venous system in short term (3 months) is similar in surgery and foam sclerotherapy.
2. Clinical improvement as measured by CEAP class and venous severity score are similar in both groups
3. Complications in both the groups are minor and relatively less frequent
4. Foam sclerotherapy is less time consuming and less morbid than surgery
5. Patients undergoing foam sclerotherapy returned to work earlier
6. Foam sclerotherapy is significantly cheaper than surgery.

10 Clinical Significance and role for further trials

- Foam sclerotherapy is a safe, simple, cost effective treatment for varicose veins
- Foam sclerotherapy is a promising alternative to surgery in the management of chronic venous insufficiency
- Since the sample size is small and follow up period is short, long-term and large scale studies have to be done before foam sclerotherapy could be considered the gold standard in the management of chronic venous insufficiency

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Appendix 1

RANDOMIZED CONTROLLED STUDY COMPARING CONVENTIONAL SURGERY AND ULTRASOUND GUIDED FOAM SCLEROTHERAPY FOR PRIMARY SUPERFICIAL VENOUS INSUFFICIENCY

PROFORMA FOR PATIENTS UNDERGOING ULTRASOUND GUIDED FOAM SCLEROTHERAPY

Name: Age: Sex: Male/ Female

Hospital No.: Serial No.:

Address:

Phone No.:

Date of Procedure: Date of follow up:

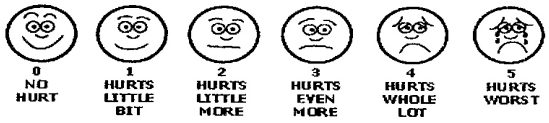
	At presentation	After 3 months	6 months	12 months	18 months	24 months
CEAP						
Clinical Score						
Ulcer size						

CLINICAL ASSESSMENT:

CEAP CLINICAL CLASS:

Clinical			At presentation		After 3 months	
			Right	Left	Right	Left
CLINICAL SCORE						
No visible signs of venous disease		0				
Telangiectasia or reticular		1				
Varicose veins		2				
PAIN	None	0				
Edema		3				
Moderate, no analgesics		1				
Skin changes		4				
Severe, analgesics required		2				
Skin changes + healed ulcer		5				
EDEMA	None	0				
Skin changes + active ulcer		6				
Asymptomatic	Mild, moderate	1				
Symptomatic	Severe	2				
VENOUS CLAUDICATION	None	0				
	Mild, moderate	1				
	Severe	2				
PIGMENTATION	None	0				
	Localized	1				
	Extensive	2				
LIPODERMATOSCLEROSIS	None	0				
	Localized	1				
	Extensive	2				
ULCER, SIZE	None	0				
	< 2 cm diameter	1				
	> 2cm diameter	2				
ULCER, DURATION	None	0				
	< 3 months	1				
	> 3 months	2				
ULCER, RECURRENCE	None	0				
	Once	1				
	More than once	2				
ULCER, NUMBER	None	0				
	Single	1				
	Multiple	2				
TOTAL CLINICAL SCORE						

PAIN SEVERITY SCORE:



Pre procedure	1st day	1 week

VENOUS DOPPLER FINDINGS:

	At admission	At 1 week	After 3 months
DVT	NA		
SFJ(Size)			
GSV(Calibre)			
SPJ(Size)			
Perforators (Number)			
Deep Venous Reflux			

Volume of foam injected:

COMPLICATIONS:

Complications	Yes/No	Description
Allergic reactions		
Cough		
Visual disturbances		
Tenderness		
Haematoma		
Hyperpigmentation		
Ulcers / others		

No. of sittings required for obliteration of GSV/SSV:

Time to return to work:

Total hospital cost:

Appendix 2

INFORMED CONSENT DOCUMENT

Patient Information:

You have been diagnosed to have primary venous insufficiency of lower limbs. This is a condition in which the valves in the veins become leaky so that high pressure blood from deep veins enters the superficial veins. This causes varicose veins, skin changes, swelling of leg and ulceration, if left untreated.

At present there are two modalities of treatment available for this condition, surgery and foam sclerotherapy.

Surgery:

This is the routine treatment which is done for varicose veins.

The procedure:

An incision (cut) is made at groin to find the junction of great saphenous (superficial) vein and femoral (deep) vein which is disconnected. Some of the tributaries of the great saphenous vein will also be ligated.

The great saphenous vein is then stripped (removed) to just below the knee. Then removal of varicose veins in the lower leg is done via multiple small cuts(avulsions).

Groin wound is closed with sutures and avulsion wounds heal without sutures.

At the end of the operation, compression bandages are applied to the leg to prevent bleeding and bruising. This operation usually takes 45 to 60 minutes for each leg.

This is usually done under spinal anaesthesia in which an injection is given at your back which temporarily blocks your sensation below the waist.

This procedure will be done by the consultant vascular surgeon/ general surgeon or surgical registrar. The surgeon who has seen you in the OPD and the one who performs the operation may not be the same.

Serious or frequently occurring risks:

• Removing varicose veins always produces some bruising and soreness. The severity of this depends on how many veins are removed. Sometimes, it can take several weeks for all the bruising to settle completely.

• Because the main wound is in the groin, this area can become infected, which can usually be treated by a course of antibiotics. The same applies to other wounds on the leg.

• Small nerves lying next to the veins can be disturbed, which can lead to patches of numbness in the lower leg and foot in 10 to 20% of patients. This usually resolves over the first year after surgery but occasionally, it is permanent.

• Rarely, a deep vein thrombosis (blood clot; DVT) can occur in the deeper veins of the leg and, occasionally, this can lead to a pulmonary embolus (blood clot to the lung). Blood clots on the lung can be fatal. Thrombosis occurs in less than 0.1% of patients.

• Varicose veins can grow back (recur), usually by regrowth of the veins. After 5 years, 10% of patients can have this recurrence.

Ultrasound guided foam sclerotherapy:

The procedure:

Ultrasound guided sclerotherapy usually involves injection of foam into the saphenous vein - most commonly from the groin to the knee. This procedure will be done by a sclerotherapist radiologist.

No anaesthesia will be given. After the procedure, an elastocrepe bandage is worn for 72 hours continuously and 6 weeks during the day only. A 60 minute daily walk is mandatory in first week.

You will be reviewed one week after the initial sclerotherapy and if necessary you may need to undergo one more injection.

The most common side effects experienced with UGS are:

1. Blood trapping: In large varicosities some blood can be trapped inside the vein. The body takes two to three months to break down and reabsorb the blood. In the meantime the vein can feel hard and can look lumpy. Occasionally the trapped blood can make the vein feel tender. This is usually transient but if it persists it may be better to have the blood removed - this is best done four to six weeks after treatment.

2. Hyperpigmentation: Approximately 10% of patients who undergo UGS notice light brown streaks over the treated veins after treatment.

3. Phlebitis: In about 1% of cases.

Rare possible side effects after UGS include:

1. Ulcers: They consist of a small ulceration at the injection site that heals slowly over one to two months.

2. Allergic reactions: Very rarely a patient may have an allergic reaction to the sclerosant.

3. Transient visual disturbance: This is experienced as black areas in the field of vision. They may last for a few minutes. It occurs in less than 0.3% of patients.

4. Telangiectatic matting: This refers to the development of new tiny blood vessels around the treated vessel and occurs in less than 2% of patients

5. Ankle swelling: Ankle swelling may occur after treatment of blood vessels in the foot or ankle. It usually resolves in a few days and is lessened by wearing the prescribed compression hosiery.

6. Deep Vein Thrombosis (DVT): This is a very rare complication, seen in approximately 1 out of every 7000 patients treated for varicose veins greater than 3 to 4mm in diameter. The possible dangers of DVT include the possibility of a pulmonary embolus (a blood clot to the lungs) and postphlebitis syndrome, in which the blood clot is not carried out of the legs, resulting in permanent swelling of the legs.

7. Risk of stroke: One case of transient monoparesis (weakness in one limb) due to foam embolization has been reported. This was due to an abnormal communication between right and left side of the heart (patent foramen ovale) which is present in upto 27% of the population.

The recurrence rates after UGS are similar to but little higher than surgery.

If you are willing to participate in our study comparing surgery with foam sclerotherapy for the treatment of varicose veins, you will be randomly assigned to one of the treatment groups i.e. you will have equal chance of receiving either one of the treatments.

It is not compulsory to participate in this study.

If you want one of the treatments specifically, you will not be part of our study but will receive the best of our care in the required treatment.

You may choose to withdraw from our study at any time but will still get the appropriate treatment.

CONSENT:

I have been informed to have primary venous insufficiency of my right and / or left lower limb(s) and the need for definitive management with surgery or foam sclerotherapy, in a language which I can understand.

I agree to participate in the study comparing surgery and foam sclerotherapy voluntarily.

I am willing to undergo either surgery or foam sclerotherapy according to the randomization.

I am fully aware of the complications of both the procedures

I understand that I can choose any one of two procedures according to my wish and still receive the best care but will not be part of the study in that case.

I understand that the doctor whom I consulted initially may not necessarily be operating / doing sclerotherapy on me and being a teaching institution, doctors in surgical training may also be part of the team.

I may choose to withdraw from this study at any time without any negative consequences.

Date: (Patient's name and signature)

(Doctor's name and signature)